UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/701,236	11/04/2003	Brenda F. Baker	ISIS-5207	5280

32650 7590 07/25/2007

WOODCOCK WASHBURN LLP
CIRA CENTRE, 12TH FLOOR
2929 ARCH STREET
PHILADELPHIA, PA 19104-2891

EXAMINER	
VIVLEMORE, TRACY ANN	

ART UNIT	PAPER NUMBER
1635	

MAIL DATE	DELIVERY MODE
07/25/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/701,236	BAKER ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 May 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,9,59,62 and 68-72* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1,9,59,62 and 68-72* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/11/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Any rejection or objection not reiterated in this Action is withdrawn.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 11, 2007 has been entered.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. 120 as follows:

The later-filed application must be an application for a patent for an invention which is also disclosed in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the

requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

Claim 62 of the instant application is directed to a method of inhibiting gene expression in a cell *in vitro* by administering a composition comprising two chemically synthesized oligomers that are at least partially complementary and comprises at least one sugar surrogate wherein one of the oligomers is capable of hybridizing with a target nucleic acid. The instant application claims priority to application 08/870,608. The sole disclosure of duplex RNAs in the '608 specification is in example 27, which describes the use of short duplex RNAs as artificial substrates in the purification and characterization of dsRNAses from rat liver cytosolic and nuclear extracts. The specification of the '608 application provides no support for the use of these artificial substrates for the purpose of inhibiting gene expression. Therefore, the priority date accorded claim 62 of this application is November 5, 2002, the filing date of application 60/423,760. If applicant believes 08/870,608 provides support for claim 62 it should be pointed out with particularity in any response to this action.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 9, 59 and 68-72 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 8, 19-22, 54, 57 and 63 of copending Application No. 10/700,697. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '697 application are directed to modified duplex RNAs comprising 2'-substitutions, which are a species that anticipates the claims of the instant application, which are directed generically to duplex RNAs comprising sugar surrogates.

The term sugar surrogate is not explicitly defined in the instant specification, but is described only by exemplification. Contemplated sugar surrogates include arabino nucleotides, pyrrolidine nucleotides and 4'-thioribose nucleotides. In view of the lack of an explicit definition for the term sugar surrogate, this term is interpreted as any entity other than the naturally occurring ribose nucleoside that is capable of use in an oligonucleotide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 9, 59 and 68-72 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1,7-9,16,18-22,26-31,73 and 76-85 of copending Application No. 10/701,264. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '264 application are directed to modified duplex RNAs comprising 2'-OMe substitutions, which are a species that anticipates the claims of the instant application, which are directed generically to duplex RNAs comprising sugar surrogates. The term sugar surrogate is not explicitly defined in the instant specification, but is described only by exemplification. Contemplated sugar surrogates include arabino nucleotides, pyrrolidine nucleotides and 4'-thioribose nucleotides. In view of the lack of an explicit definition for the term sugar surrogate, this term is interpreted as any entity other than the naturally occurring ribose nucleoside that is capable of use in an oligonucleotide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 9, 59 and 68-72 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 9, 11, 75, 78 and 93-97 of copending Application No. 10/701,316. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '316 application are directed to modified duplex RNAs comprising 2'-substitutions, which are a species that anticipates the claims of the instant application, which are directed generically to duplex RNAs comprising sugar surrogates. The term sugar surrogate is not explicitly defined in the instant specification, but is described only by exemplification. Contemplated sugar surrogates include arabino nucleotides, pyrrolidine nucleotides and 4'-thioribose nucleotides. In view of the lack of an explicit definition for the term sugar surrogate, this term is interpreted as any entity other than the naturally occurring ribose nucleoside that is capable of use in an oligonucleotide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 1 and by dependence claims 9, 59 and 68-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite because it recites an oligomeric compound that is only required to be about 12 nucleotides in length that nevertheless must have at least 17 nucleobases complementary to a target nucleic acid.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 9, 59 and 68-70 are rejected under 35 U.S.C. 102(a) as being anticipated by Bevilacqua et al. (Biochemistry 1996).

The claims are directed to compositions comprising chemically synthesized oligomers that comprise about 12 to about 30 nucleotides, are not covalently linked and are at least partially complementary to each other; at least one strand is partially complementary to a target nucleic acid. Each strand comprises at least one sugar surrogate and at least one strand has a plurality of 2'-hydroxy-pentofuranosyl sugar

moieties. In specific embodiments the ribonucleotides are in the second oligomer, the oligomers are chimeric oligonucleotides that may be gapmers or hemimers, are formulated with a pharmaceutically acceptable carrier, are complementary over at least 17 contiguous nucleotides or are about 15 to about 25 nucleotides in length.

Bevilacqua et al. disclose (see figure 5 and description on page 9988, first column) chimeric dsRNA duplexes that correspond to the 22 nucleotides of the TAR gene. Each strand contains areas of 2'-OMe substitutions and ribonucleotides, making chimeric oligonucleotides comprising two regions of nucleosides of two different types. Gapmers, 5'-hemimers and 3'-hemimers are defined as having one or more terminal segments with nucleosides of a first type and a further segment with nucleosides of a second type. The use of the open language "comprising" in the definition of the chimeric oligonucleotides allows for the presence of additional regions, therefore the dsRNAs meet the limitations of claims 21, 22 and 26-31. This duplex is used in to probe the sequence recognition of the enzyme PKR, which involves formulation of the duplex as a composition with a pharmaceutically acceptable carrier.

Thus, Bevilacqua et al. disclose all limitations of and anticipate claims 1, 9, 59 and 68-70.

Claims 1, 9, 59 and 68-70 are rejected under 35 U.S.C. 102(a) as being anticipated by Yu et al. (RNA 1997).

The claims are directed to compositions comprising chemically synthesized oligomers that comprise about 12 to about 30 nucleotides, are not covalently linked and are at least partially complementary to each other; at least one strand is partially

complementary to a target nucleic acid. Each strand comprises at least one sugar surrogate and at least one strand has a plurality of 2'-hydroxy-pentofuranosyl sugar moieties. In specific embodiments the ribonucleotides are in the second oligomer, the oligomers are chimeric oligonucleotides that may be gapmers or hemimers, are formulated with a pharmaceutically acceptable carrier, are complementary over at least 17 contiguous nucleotides or are about 15 to about 25 nucleotides in length.

Yu et al. disclose in figure 1C a duplex comprising one strand of RNA corresponding to a 24-nucleotide portion of 28S ribosomal RNA with one 2'-OMe substitution. The other strand of the duplex is 18 nucleotides in length and comprises a chimeric gapmer oligonucleotide of 2'-OMe and 2'-deoxy nucleotides. 5'-hemimers and 3'-hemimers are defined (see claims 27 and 30) as having a terminal segment with nucleosides of a first type and a further segment with nucleosides of a second type. The use of the open language "comprising" in the definition of the hemimer allows for the presence of additional regions, therefore the gapmer molecule meets the limitations of claims 26-31. This duplex is used in an RNase H cleavage assay, which involves formulation of the duplex as a composition with a pharmaceutically acceptable carrier.

Thus, Yu et al. disclose all limitations of and anticipate claims 1, 9, 59 and 68-70.

Claim 62 is rejected under 35 U.S.C. 102(e) as being anticipated by Brown et al. (US 2004/0029275, of record).

The claim is directed to a method of decreasing expression of a target gene using a composition comprising chemically synthesized that are not covalently linked and are at least partially complementary to each other wherein each strand comprises

at least one sugar surrogate and at least one strand has a plurality of 2'-hydroxy-pentofuranosyl sugar moieties.

Brown et al. disclose siRNAs and methods of using these siRNAs to inhibit gene expression. At paragraphs 21-22, Brown et al. disclose that the siRNAs can be 15-1000 nucleotides in length and can comprise one or two strands. At paragraph 152 they disclose the siRNAs of the invention comprise modified nucleotides that include derivatives or analogs of 5 carbon sugars.

Thus, Brown et al. disclose all limitations of and anticipate claim 62.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 9, 59 and 68-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Beigelman et al. (Journal of Biological Chemistry 1995) in view of Koizumi et al. (Nucleic Acids Research 1989, cited on IDS of 5/07) and Stec et al. (US 5,151,510).

The claims are directed to compositions comprising chemically synthesized oligomers that comprise about 12 to about 30 nucleotides, are not covalently linked and are at least partially complementary to each other; at least one strand is partially complementary to a target nucleic acid. Each strand comprises at least one sugar surrogate and at least one strand has a plurality of 2'-hydroxy-pentofuranosyl sugar moieties. In specific embodiments the ribonucleotides are in the second oligomer, the oligomers are chimeric oligonucleotides that may be gapmers or hemimers, are formulated with a pharmaceutically acceptable carrier, are complementary over at least 17 contiguous nucleotides or are about 15 to about 25 nucleotides in length or comprise at least one phosphorothioate linkage.

Beigelman et al. teach systematic chemical modification of hammerhead ribozymes to optimize the structure, nuclease resistance and catalytic activity of this ribozyme. Beigelman et al. teach that the optimized ribozyme is about 30 nucleotides in length and comprises 2'-OCH_3 substituted nucleotides flanking a region of ribonucleotides and therefore comprises both a gapmer and 5' and 3' hemimers. This ribozyme will hybridize to a substrate sequence and therefore is an antisense strand that is at least partially complementary to a target nucleic acid. Beigelman et al. do not teach this ribozyme in a composition comprising a second strand containing at least one

2'-OCH_3 substitution, nor do they teach that at least 17 nucleobases hybridize to the substrate.

Koizumi et al. teach a hammerhead ribozyme substrate sequence that is about 12 to about 30 nucleotides in length that is at least partially complementary to a hammerhead ribozyme and comprises a plurality of ribose nucleotides and at least one 2'-OCH_3 substituted nucleotide. Koizumi et al. teach on page 7064 that this substrate is incapable of being cleaved by a ribozyme and further teach the availability of non-cleavable ribozyme complexes is useful for structural studies of metal ion dependent cleavage of RNA.

It was well known in the art at the time the invention was made to incorporate a phosphorothioate linkage into an oligonucleotide for the purpose of increasing stability and nuclease resistance. See for example, Stec et al. who teach the use of phosphorothioate linkages for these desirable properties.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to form a composition comprising the 2'-OCH_3 substituted hammerhead ribozyme of Beigelman et al. and the non-cleavable substrate of Koizumi et al. in order to perform structural studies on the 2'-OCH_3 substituted ribozyme. Koizumi et al. provide a motivation and reasonable expectation of success in forming such a complex by teaching that the non-cleavable substrate is useful for structural studies of ribozymes and that this substrate forms a complex with a ribozyme but is not cleaved. It would further have been obvious to produce a ribozyme and substrate that have at least 17 base pairs of complementarity and comprise phosphorothioate linkages. One of ordinary skill in the art would recognize that inclusion of

phosphorothioate linkages and production of ribozyme and substrate with a particular degree of complementarity to be design choice made in the course of routine optimization and that ribozyme-substrate complexes with a greater degree of stability and complementarity provide a more stable complex for use in structural studies such as crystallization.

Thus, the invention of claims 1, 9, 59 and 68-72 would have been obvious, as a whole, at the time the invention was made.

Claims 1, 9, 59 and 68-72 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yu et al. as applied to claims 1, 9, 59 and 68-70 above, and further in view of Stec et al. (US 5,151,510).

Claims 1, 9, 59 and 68-70 are described in the 102 rejection over Yu et al. Claims 71 and 72 recite that one or both of the oligomeric compounds of the composition have at least one phosphorothioate linkage.

Yu et al. disclose a duplex RNA comprising 2'-OMe substitution and a plurality of ribonucleotides as described fully in the 102 rejection over this reference. Yu et al. do not teach their duplex as containing phosphorothioate linkages.

It was well known in the art at the time the invention was made to incorporate a phosphorothioate linkage into an oligonucleotide for the purpose of increasing stability and nuclease resistance. See for example, Stec et al. who teach the use of phosphorothioate linkages for these desirable properties.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to produce the duplex taught by Yu et al. with phosphorothioate

linkages. One of ordinary skill in the art would have had a motivation and reasonable expectation of success in doing so based on the recognition in the art that use of phosphorothioate linkages provides the advantages of increased stability and nuclease resistance.

Thus, the invention of claims 1, 9, 59 and 68-72 would have been obvious, as a whole, at the time the invention was made.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, J. Douglas Schultz, can be reached on 571-272-0763. The central FAX Number is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has

been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Tracy Vivlemore
Examiner
Art Unit 1635

TV
July 20, 2007